BioDiscovery 19: e9076
doi: 10.3897/BioDiscovery.19.e9076

OPEN ACCESS

Review Article

The success of stem cell transplantations and the potential post-transplantation complications may be dependent, among other factors, on the capacity of the recipient and the transplanted cells to repair DNA damage

Lewis Reynolds ‡

‡ CMCBR, School of Science Engineering and Technology, Abertay University, Dundee, United Kingdom

Corresponding author: Lewis Reynolds (lewis-reynolds@hotmail.co.uk)

Received: 03 May 2016 | Accepted: 28 Mar 2016 | Published: 29 Mar 2016

Citation: Reynolds L (2016) The success of stem cell transplantations and the potential post-transplantation complications may be dependent, among other factors, on the capacity of the recipient and the transplanted cells to repair DNA damage. BioDiscovery 2016; 19: 1; doi: 10.3897/BioDiscovery.19.e9076

Abstract

Cell therapy is presently a treatment of choice for many types of haematological and metabolic diseases and is likely to become a therapeutic option for other severe human diseases and conditions in the near future. The success of cell transplantation depends on a variety of factors, including the degree of HLA match between the donor and the recipient, the infectious burden of the graft, cell dosage, age, general state of the recipient and other incompletely characterised features of the donor and the recipient. It is likely that the individual capacity for identification and repair of DNA damage and maintenance of genomic integrity may account, at least in part, for these elusive factors that modulate transplantation outcome in terms of success rate and both long and short term post-transplantation complications. This paper outlines the role of individual repair capacity of the donor and recipient in cell transplantations, summarising the little knowledge already accumulated in the field whilst analysing the known major issues of the use of different types of stem cells. Attention will be given to their capacity to maintain the integrity of their genome, the ability to renew their own population, differentiate into various cell types and in

© Reynolds L. This is an open access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

some cases, succumb to carcinogenic transformation. Analysis of the individual capacity may become a useful tool in the assessment of the suitability of a set of freshly collected stem cells or an *in vitro* propagated cell line for potential clinical applications.

Keywords

Cell therapy, individual repair capacity, stem cells, transplantation, DNA damage

1. Transplantation of Cells and Tissues - from desperate measures to (almost) complete cures for severe terminal disease

The idea of treating physical disease or reconstructing injured tissue by transplantation of healthy tissues and organs has fascinated clinicians throughout human history. There is sufficient evidence that the surgical techniques needed for harvesting and transplantation of skin were already developed in the past (Kiel 1978). Very early on however, it was noted that cross-transplantation between different individuals were unsuccessful; therefore the attempts to cure by transplantation were, up to the beginning of the 20th century, limited to auto-transplantation of tissues (mostly skin, but occasionally bone in rare circumstances). The advent of allogenic tissue transplantations began in 1905 with the successful transplantation of the cornea, performed by Eduard Zirm. Zirm used an enucleated eye from an unrelated donor, to a recipient with bilateral chemical burns of the cornea (Armitage 2006). The surgery could be described as 50% successful as the transplant in one eye was rejected, but a success in the other, resulting in significant improvement of visual activity of the recipient. The decades following this ground-breaking intervention however were disastrous, with many attempts at transplantation of organs and tissues between unrelated donors and recipients almost invariably ending in disaster. Henceforth, transplants were generally limited to procedures performed between genetically identical individuals (monozygotic twins), however there are some 'last resort' attempts to save the life of the terminally ill with transplantations from living or cadaveric donors, with the latter being generally unsuccessful. The first successful transplantation of haematopoietic stem cells (HSCs) from bone marrow were conducted in 1956 by a team under Edward Donnell Thomas in New York, USA. The donor and recipient in this case were identical twins.

There have been several documented attempts to alleviate aplastic anaemia resulting from acute irradiation incidents by infusion of bone marrow suspensions from related or unrelated donors, however each instance has been, on the whole, unsuccessful and the reasons for this are unclear (Cosset 2002). Once the material carriers of biochemical individuality were discovered, thanks to the works of Jean Dausset and Rose Payne (DAUSSET and BRECY 1957, Payne and Hackel 1961, it became clear that the first and foremost determinant of the success of any type of allogenic transplantation was the degree of tissue compatibility between the donor and the recipient. It was from this point on

that reliable identification of compatible donor-recipient pairs became one of the major tasks of clinical and transplantation science. This allowed, on one hand, for the assessment of potential success of the transplantation before intervention whilst on the other hand, allowing for the development of approaches to induce the recipients' tolerance of allogenic transplants. This methodology for HLA typing has been developing steadily in the second half of the 20th century, allowing resolution up to allele level. As a result, the number of transplantations of cells, tissues and organs (on occasion, more than one organ in a single transplantation) has been increasing since the 1970's.

The type of cells most commonly used for transplantations (historically and today) are haematopoietic stem cells obtained from the bone marrow or peripheral blood from adult donors, or cord blood collected at birth. Over the last few decades, transplantations of haematopoietic stem cells have become have become an option of choice in the treatment of haematological malignancies, aplastic anaemia, myelodysplastic syndrome, severe immune deficiencies and some types of metabolic disorders, provided that a matching transplant is readily available or likely to be shortly. The average waiting time for finding a potential match in the donor databases has decreased in the last decades (usually from weeks to months in some cases, however this may be longer in ethnic groups) and has been greatly facilitated by the improved communication between different centres, allowing identification of a suitable donor with a single search in multiple databases. For 2014, over 40,000 transplantations of HSCs performed in 47 countries were reported (Passweg et al. 2016). Nevertheless, HLA haplotype diversity of stored HSCs is still an issue, especially for minority ethnic groups and individuals of mixed ancestry. Within the last 15 years, much research has been conducted into the potential clinical use of mesenchymal stem cells (MSCs), embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) as they provide opportunities for a source of more than one type of differentiated cells (in the case of ESCs, virtually all types of differentiated cells of the human body). Indeed, HSC transplantations are saving lives today, whereas the transplantations of MSCs are still at a clinical trial level, with ESCs still very much so a far cry from clinical use. At present, it is believed that it is only a matter of time and effort before cell therapy becomes a principal treatment for many more severe and previously incurable conditions.

There have always been significant concerns about the safety of cell therapies. Originally, these were mainly concerns about transmission of blood-borne infections. The case of David Vetter in 1983 however resulted in an increase of these safety concerns. As it had turned out, it was not only known pathogens (such as hepatitis B and C viruses, and later, HIV) that could compromise the safety of the recipient, but also infectious agents that were, in immunocompetent individuals, easily kept in check such as the Epstein-Barr Virus (EBV), Cytomegalovirus (CMV) and others. With the advancement of HSC-based therapies it became clear that not only the degree of compatibility between the donor and the recipient, but also the number of cells per kilogram of body weight of the patient (cell dose) mattered in the success of a perspective transplantation. Therefore, transplantations of even perfectly matched HSCs could be unsuccessful if the donor cells were not over a certain cell dose limit. With this, the role of alloreactive T-cells present in HSCs and organ transplants for achieving therapeutic effect in haematological malignancies and the role of

carriership of premalignant rearrangements in the genome of the cells of the graft came into focus. As it turned out, these factors may predetermine the risk of severe complications of HSC transplantations such as graft-versus-host disease (GVHD) and secondary leukaemia. When multipotent (MSCs) and pluripotent stem cells (ESCs and iPSCs) began to be contemplated as a base for development of potential therapies, multiple new safety concerns emerged. Cell preparations derived from pluripotent stem cells may contain trace amounts of undifferentiated cells with significant carcinogenic potential. With MSCs, there may be another concern related to the low rates of survival of transplanted cells, needing a repeat transplantation and may potentially result in other adverse effects. Eventually, the largest determinant of applicability for potential stem cell therapies for treatment came not from the benefit(s) to the patient, but rather the incidence and degree of adverse effects from the therapy.

It was then clear early on that whether the transplanted cells would engraft and whether they would cause short or long term benefits (or detrimental effects) depended on inherent characteristics of the tissues of the donor and the recipient. These characteristics apparently extended beyond tissue compatibility and carriership of infectious agents (although these are important) and are related essential factors that determine the chances of survival of the donor cells in an allogenic environment and have the capacity to generate differentiated progeny that may repopulate cell niches in the recipient. There may yet be another factor determining the chances for success in cell and transplantations that is still largely underestimated; namely, the individual capacity of repair of DNA damage (individual repair capacity, IRC). Essentially, the capacity of a cell to proliferate is determined by its capacity to detect and repair any damage to its DNA, as DNA is a very potent signal for enforcement of cell cycle arrest, DNA repair and/or apoptosis. At the same time, the carcinogenic potential of a cell is also determined by the capacity for DNA repair, as carcinogenesis results from accumulation of discrete molecular events that, each taken separately, are subject of control of the cellular mechanisms of checking for the presence of genomic damage and the management of genomic integrity. Analysis of the individual repair capacity of the cells in a graft, and of the recipient of allogenic cells and tissues may provide additional information about the chances of success of the transplantation and the potential adverse effects for the particular patient. This may allow a ‘fine-tuning’ of the therapeutic strategy in order to suit the individual needs of the patient.

2. The Discovery of Individual Repair Capacity

In the last third of the 20th century, DNA repair proved itself as a fundamental process in living cells, probably no less important as the triad of replication, transcription and translation that made up the famous central dogma of molecular biology as formulated by Francis Crick in 1970. After it became clear that a molecular defect in a single gene coding for a protein functioning in DNA repair could be associated with severe early-onset systemic disease (CLEAVER 1968), and later, that inherited defects in the tumour-suppressor gene RB1 were associated with development of retinoblastoma (Fung et al. 1987), it was believed that all genetic alterations that affected genes of DNA damage

detection and repair had immediate adverse effects on the phenotype. This meant that there could be very little degree of polymorphism in genes coding for proteins of DNA repair and maintenance of genomic integrity. Even before the discovery of the first 'disease of DNA repair' (xeroderma pigmentosum, defined as a disease of DNA repair by Cleaver in 1968), it was reported that exposure to environmental carcinogens such as tobacco smoke resulted in very different rates of occurrence of lung cancer in age-matched males and females (Haenszel et al. 1962, Haenszel and Taeuber 1964). It was then shown that cultured lymphocytes isolated from clinically healthy human volunteers repaired damage at very different rates, with lymphocytes isolated from females showing generally superior performance with regard to removing DNA damage than lymphocytes isolated from age-matched males (Pero et al. 1978, Pero and Östlund 1980). Clearly, there was individual variance in the capacity to repair genotoxic damage determined by genetic makeup of the individual, but the individual components were not known before the early 1990s, when a gene previously known to be mutated at a high rate in human cancers was identified as the culprit in a rare hereditary cancer syndrome (Li-Fraumeni syndrome) (Baker et al. 1989, Malkin et al. 1990) was found to contain a very common polymorphism that was not associated with any immediate effects on the phenotype (namely, the Pro72Arg polymorphism in the TP53 gene, rs1042522) (Ara et al. 1990). Later, it was shown that carriership of either allele of the TP53 Pro72Arg polymorphism showed significant variance in the biological properties of the resultant p53 protein (Thomas et al. 1999). This was only the beginning of the studies on the role of IRC in human health and disease. It had later become clear that the capacity for DNA repair and management of genomic integrity in humans could have significant effects on the risk for development of many common diseases with late onset, such as diabetes and cancer (Roy et al. 2007, Petkova et al. 2011b, Schiewer and Knudsen 2016), cardiovascular disease (Chelenkova et al. 2014, Wu and Roks 2014), neurodegenerative disease (Coppedè and Migliore 2015, Nayyar et al. 2015); and that it could potentially reflect on the susceptibility for disease in different individuals, and at different ages (Cherdyntseva et al. 2010, Chakarov et al. 2012, Petkova et al. 2013) and the outcomes of different genotoxic treatments (Kan and Zhang 2015, Velic et al. 2015, Petkova et al. 2014b). DNA damage repair pathways began to be regarded as useful therapeutic targets in cancer therapy, (Khalil et al. 2012, Khalil et al. 2012b, Khalil et al. 2012c, Gavande et al. 2016). Outcomes of genotoxic therapies with myeloablative intent and the potential complications of therapy with haematopoietic stem cells were found to depend on the capacity of the recipient to repair the damage inflicted by myeloablative regimens (Arora et al. 2010). With the development of methodologies for derivation and maintenance of stem cells in culture emerged issues related to the 'stemness' characteristics of cultured stem cells, including preservation of their potential for proliferation and differentiation and the minimisation of the carcinogenic properties of cells with inherent tumorigenic potential such as ESCs and iPSCs. All these aspects of the biology of cultured stem cells are directly dependent on their capacity of cultured cells to detect and repair genomic damage. With the rapid increase of the number of stem cell lines available for research and, potentially, for clinical applications, analysis of the individual capacity for repair of DNA damage may be helpful in identification of cell lines that are likely to proliferate stably in culture with minimal risk of cancerous transformation. The interest in the role of IRC in stem cell biology, and potentially as a factor for their use in clinical

applications in the future, has only recently begun. However, the number of published reports in the field is still low. There could be little doubt however, that the capacity to detect and repair DNA damage may become one of the key factors in the assessment of the suitability for a batch of collected haematopoietic, mesenchymal stem cells or a pluripotent cell line to be used for clinical purposes. Below we will try to summarise the present state of the scientific knowledge about the role of IRC in the success of stem cell transplantations and the potential adverse effects; and address the potential issues in the field.

3. The Role of IRC as a Factor Determining the Outcome of HSC Transplantations

Thanks to the improved methodology of HLA typing, analysis of blood-borne infections and post-transplantation therapies, the survival of patients that have had received HSCs has grown significantly. The 5-year survival rates vary between 30 and 75%, depending on the degree of HLA match, the cell dose per kg body weight of the patient, the age of the patients, their general status, the type of the underlying disease and the type of the graft (stem cells from bone marrow, peripheral blood or cord blood) (Serna 2003, Gibbons 2005, Leung et al. 2011). The prolonged post-transplantation survival brought to attention yet another type of complication in transplanted patients, namely, chronic GVHD, development of leukemia originating from donor cells and, in autologous transplantation for treatment of haematological malignancies, recurrence of the initial disease because the autologous cells contained the transformed clone. As it turned out, individual capacity of repair of DNA damage may be another factor determining the chances for success of HSC transplantations. On the one hand, this is related to the fact that the recipient of HSCs is more often than not subjected to genotoxic treatments in order to achieve partial or complete myeloablation. Individuals with IRC that are lower than average (sometimes even subtly lower) may exhibit severe, even life-threatening adverse effects from myeloablative regimens, even if they are generally well-tolerated, and may be still left with a considerable amount of tissue damage at the time of transplantation. The latter may be associated with severe post-transplantation complications such as high-grade GVHD. On the other hand, an inferior capacity for repair of DNA damage in the cells of the graft, coupled with the lifelong immunosuppressive regimens that are usually administered to patients with transplanted tissues and organs, may increase the risk of development of malignancies originating from donor cells. An assessment of the individual repair capacity of the recipient (ideally, before and at the end of the myeloablation cycle) and of the cells in the graft may potentially assist the clinician in the decision-making of the eligibility of the patient for certain treatments. This assessment includes an evaluation of the chances for potential benefits and the anticipation of the adverse treatment-related effects, both in the short term (treatment-associated toxicity) and in the long term (high-grade GVHD, donor cell leukaemia).

3.1 Association of Individual Capacity for Repair of Genotoxic Damage and the Risk for Development of High-Grade Graft-Versus-Host Disease (GVHD)

GVHD is a serious post-transplantation complication that develops in immunocompromised patients that have received a transplant of allogeneic immunocompetent haematopoietic cells. Unlike regular tissue and solid organ transplantations where the transplanted organ is attacked by the immune system of the host, GVHD has an immune conflict between the host and recipient in reverse, where the immunocompetent cells in the graft recognise and target the host tissues. GVHD may be acute or chronic (depending on whether it develops within 100 days of the transplantation or afterwards) and its severity may significantly vary; from mild (grade I) to severe (grade IV). GVHD typically targets three organs and systems; skin and mucosa, the liver and/or the gastrointestinal tract as a whole. Acute GVHD may be severe (sometimes life-threatening) and is generally associated with decreased survival. It is believed that the tissue injury caused by the genotoxic conditioning regimens prior to HSC transplantation is the major pathogenetic factor in the development of acute GVHD [reviewed in (Jacobsohn and Vogelsang 2007). Lower-than-average capacity for DNA damage repair may be associated with increased revels of residual tissue damage in patients undergoing myeloablation prior to HSC transplantation. One polymorphism in genes coding for proteins responsible for repair of DNA damage have already been implicated in the pathogenesis of severe (grade II-IV) acute GVHD - namely, the rs6844176 C-to-T polymorphism in subunit 1 of replication factor C (RFC-1) (Arora et al. 2010). RFC-1 is a component of the BRCA1-associated genome surveillance complex (BASC) that scans the genomic DNA for the presence of structural damage in DNA, activates damage-response pathways and recruits DNA repair machinery to the damage site (Wang et al. 2000). Recipient carriership of the 2351insT (rs41376448) allele of the HMGB1 gene (coding for a master transcription regulator protein tightly linked with DNA repair) was found to reduce the risk of moderate-to-severe acute GVHD, whereas homozygous carriership of the same allele in the donor cells was associated with chronic GVHD (Kornblit et al. 2010). Unlike acute GVHD, chronic GVHD (provided that it is kept under control) may be associated with increased survival after transplantations of allogeneic HSCs. In the study of Arora et al. cited above, carriership of the 1300+104A>G (rs1805410) polymorphism in the PARP1 gene was found to be associated with a 2-fold increase of the risk of chronic GVHD in patients with transplanted HSCs. Poly-(ADP-ribose)-polymerase family member 1 (PARP1) is damage sensor molecule that activates p53-dependent pathways in the presence of DNA breaks, induces remodelling of chromatic structure in the area of the lesion site and recruits the DNA repair machinery (Valenzuela et al. 2002). The genotoxic agents most commonly used in myeloablative regimens are alkylating agents (cyclophosphamide, ifosfamide, melphalan and others), adduct-forming agents inducing accumulation of double-strand breaks in DNA (anthracyclines, mitoxanthrone) and ionising radiation (separately or in combination). All these agents induce structural damage in DNA (base modification, strand breaks), hence the importance of the normal functioning of damage-sensing proteins and complexes for the repair of tissue damage inflicted by myeloablative regimens. Several common polymorphisms in key genes coding for proteins of the base excision repair (BER - functioning in repair of oxidised bases) have been shown to modulate treatment-related mortality (including GVHD-related mortality) in patients with

allogeneic HSC transplantations (Thyagarajan et al. 2010). Four of these polymorphisms (namely, the rs159153 C-to-T polymorphism in the promoter of the hOGG1 gene (coding for a glycosylase removing 8-oxoguanine and formamidopyrimidines from DNA), the rs3135974 A-to-G polymorphism in the LIG3 gene, coding for ligase III (the primary ligase of BER); the rs3219463 A-to-G and the rs3219476 G-to-T polymorphisms in the MUTYH gene (coding for a DNA glycosylase resolving A/G mispairs) were found to increase the risk for transplant-related mortality in patients with allogeneic transplantations of HSCs. In the same study, carriership of two other polymorphisms (rs167715 C-to-T and rs2374327 A-to-T, both in the gene TDG coding for a glycosylase catalysing the removal of T from G/T, C/T and T/T mispairs) were associated with increased chances for post-transplantation survival. Apparently, the individual capacity for repair of base modifications along with strand break repair are among the key factors determining the degree of tissue damage after conditioning regimens, and respectively, the risk for post-transplantation survival. An assessment of basic parameters of IRC and specifically, the proficiency of repair of damage managed by BER and break repair pathways may assist in the process of selection and personalisation of a conditioning and post-transplantation regimens as well as in the management of the potential adverse effects, both before and after HSC transplantation.

3.2 Association of Individual Capacity for Repair of Genotoxic Damage and the Risk for Development of Secondary Leukaemia after HSC Transplantations

After large-scale collection and storage of haematopoietic stem cells from cord blood became possible, it offered seemingly limitless opportunities for treatment of malignant haematological disease with one's own (immunologically 100 % compatible) haematopoietic cells. Thus, autologous use of HSCs was associated with particularly high hopes for successful transplantation outcomes. Soon it became apparent that for most types of childhood leukaemia, the abnormal clones carrying pre-leukemic chromosome rearrangements were already present in neonatal blood spots of infants that later developed leukaemia and therefore were likely to have arisen in utero (Gale et al. 1997). It was later confirmed that clones carrying chromosome translocations, that may later result in leukaemia, were often generated in the course of normal intrauterine development (Mori et al. 2002, Gruhn et al. 2008). Expansion of specific leukocyte clones also turned out to be quite common, as a significant proportion of healthy people were found to carry an expanded non-aberrant lymphocyte clone that amounted to >10% of the total lymphocyte population (Nakano et al. 2004). Interestingly, chromosomal aberrations commonly seen in leukaemia (monosomy 7, trisomy 8, loss of the long arm of chromosome 5 and deletions of portions of the 17p13 locus containing the TP53 tumour suppressor gene) were not identified in HSCs collected from peripheral blood of adult patients that received myeloablative treatment and subsequent autologous transplantation of HSCs from peripheral blood and went on to developing leukaemia or myelodysplastic syndrome (MDS) (Weber et al. 2000). The latter may mean that the expansion of clones with significant leukemic potential are suppressed in the course of individual life. At present, autologous HSC transplantations are not recommended for most types of leukaemia, with the possible exception of patients with acute myeloid leukaemia placed in the "favourable" and

"intermediate" risk group by cytogenetics (defined by absence of specific genomic rearrangements that are usually identified in autologous haematopoietic progenitors and the presence of less than 3 different clonal chromosomal abnormalities) (Burjanivova et al. 2006, Tummala et al. 2012, SABTY et al. 2012). In any case, the sole presence of a pre-leukemic clone in the HSCs of a healthy infant do not necessarily mean there is a 100% risk for development of leukaemia later in life. The case is completely different when HSCs are transplanted in a patient whose immune system has been significantly weakened, or altogether destroyed in the course of myeloablative treatments prior to transplantation. The functioning of the newly transplanted immunocompetent cells are suppressed by the post-transplantation therapeutic regimens. The risk for transformation of the pre-leukemic clone received with the autologous graft into an invasive leukemic clone may be greatly enhanced in immunocompromised patients, resulting in recurrence of the primary malignancy. The latter significantly decreases the potential value of autologous transplantation of HSCs in leukaemia, except in select groups. Of course, since latent chromosomal translocations with carcinogenic potential may also exist in HSCs from clinically healthy donors, donor cell leukaemia may also occur after allogeneic transplantation of HSCs from healthy donors. Several dozens of cases of leukaemia (originating from allogeneic donor cells transplanted for the purposes of treatment of leukaemia, lymphoma or aplastic anaemia) have already been reported (Neglia et al. 1991, Matsunaga et al. 2005, Bobadilla-Morales et al. 2015). The risk for development of secondary haematological malignancy is likely to be higher in autologous as well as allogeneic HSCs carrying genetic polymorphisms conferring lower-than-average capacity to repair genotoxic damage. The data about the role of polymorphisms in genes coding for key genes in DNA repair and maintenance of genomic integrity is still very limited. However there is a report on donor cell leukaemia in a recipient that received a transplant from an HLA matched sibling carrying the repair-deficient alleles of the polymorphisms XPD Lys751Gln (rs1052559) and XRCC3 Thr241Met (rs861539) in their homozygous state (Diamond et al. 2011). The XPD (ERCC2) gene codes for one of the two helicases that unwind DNA in the vicinity of the lesion site, allowing free access of the machinery for repair by nucleotide excision (NER), whereas XRCC3 codes for a key protein of repair by homologous recombination. Carriership of these two polymorphisms has already been identified as a risk factor for development of leukaemia, increasing the risk > 2-fold for XPD Lys751Gln and > 3.5 fold for XRCC3 Thr241Met, respectively (Hamdy et al. 2011, Bănescu et al. 2014). Additional research is required in order to confirm the report of Diamond et al. 2011, but it could be expected that some of the polymorphisms in other genes responsible for identification and repair of DNA damage and maintenance of genomic integrity that have been already implicated in the pathogenesis of leukaemia, such as TP53 Pro72Arg, MDM2 SNP309 (rs2279744), XRCC1 Arg194Trp (rs1799782), hOGG1 Ser326Cys (rs1052134), CCNH Val270Ala (rs2230641) (Enjuanes et al. 2008, Batar et al. 2009, Do et al. 2009, Li et al. 2011) and polymorphisms that have been associated with differential outcomes after haematological disease and HSC transplantations (the above mentioned TP53 Pro72Arg and also HMGB1 3814 C-to-G (rs2249825); XPC Lys939Gln (rs2228001) and XPF C673T (Kornblit et al. 2010, Xu et al. 2012, McGraw et al. 2015, Bănescu et al. 2016) and potentially, others may modulate the risk for development of donor-cell leukaemia in patients with HSC transplantations. Carriership of the variant (deletion) allele

of the -1377delA (rs41369348) polymorphism in the HMGB1 gene was associated with 2-fold increased risk of relapse of the primary haematological malignancy (Kornblit et al. 2010).

Recently, it was reported that deficiency of exonuclease 1 (functioning in 5'- end resection of DNA ends, a key enzyme activity in mismatch repair and repair by homologous recombination) had no effect on quiescent murine HSCs, but in dividing HSCs resulted in increased sensitivity to DNA damage and rapid cell death after genotoxic challenge (Desai et al. 2014). Thus, deficiencies of EXO1 conferred by carriership of genetic polymorphisms may have little or no effect in healthy individuals (maintaining the majority of their HSC population in the quiescent state at any given time) but may have significant effect when EXO1-deficient cells have been transplanted and stimulated into rapid proliferation. Several polymorphisms in the human EXO1 gene have been described so far (Glu589Lys (rs1047840), Leu757Pro (rs9350), and others) that were related to increased propensity to cancer (Jin et al. 2008, Bau 2009, Haghighi et al. 2010); therefore, it is possible that EXO1 polymorphisms may play a role in both the chances for engraftment of HSCs and the risk for secondary malignancies after transplantation.

4. Potential Role of IRC as a Factor Determining the Survival of Transplanted Mesenchymal Stem Cells

Mesenchymal stem cells are a specific type of multipotent cells originating from the embryonic mesenchyma. MSCs may be isolated from the amniotic fluid, the Wharton's jelly of the umbilical cord, the placenta, the stroma of the adult bone marrow, the dental pulp and the gingiva. MSCs are not defined by strict criteria (e.g. expression of a specific surface receptor) but are, in fact, rather a heterogeneous population. They adhere to plastic surfaces in vitro, are capable of spontaneous differentiation along the osteogenic, chondrogenic and adipogenic lineages and express a subset (but not all) of the surface markers of the skin and lung fibroblasts (Dominici et al. 2006). Targeted differentiation of MSCs may yield other cell types as well, such as insulin-producing pancreatic cells, different kidney-specific cell types such as tubulocytes and podocytes, cardiomyocytes, and other cell types (Sun et al. 2007, Pereira et al. 2008, Brunner et al. 2008, Asanuma et al. 2010). MSCs possess significant potential for use in the regenerative and reparative medicine because of their versatility. At the same time, they present significantly less ethical challenges than embryonic stem cells with regard to their collection. Their proliferative potential is higher compared to somatic cells but is nowhere near to the capacity for proliferation as ESCs; therefore, their use is expected to be associated with much less potential adverse effects than ESCs. There are, however, two serious limitations to the use of MSCs in clinical applications; their poor viability after transplantation in injured tissues and their poor migratory capacity, meaning that their beneficial effects may be short-lived and are unlikely to extend beyond the narrow limits of the lesion site (Lee et al. 2015). In animal models of ischemic myocardial infarction, less than 6 % of the autologous MSCs injected at day 0 were identifiable by day 10 in pigs (Gyongyosi et al. 2008). In immunodeficient mice, the results are even poorer, with < 0.5 % of the transplanted human

MSCs surviving by day 4 post-transplantation (Toma 2002). In a small group of human patients with myocardial infarction that received intracoronary infusion of MSCs, no more than 2.5 % of the infused cells were identifiable at the lesion site within 75 minutes post-infusion (Hofmann 2005. This and other similar reports brought about the concept that the MSC did not actually integrate stably within the injured tissue but, rather, exerted a stimulating effect on the regenerative processes at the lesion site (neo-angiogenesis in myocardial injury, axonal regeneration in spinal cord injury, etc.), then habitually die (Kamada et al. 2005, Tang et al. 2009, Poncelet et al. 2010). Better results have been recently obtained with human bone marrow and umbilical cord MSCs transplanted in rat spinal cord injury models, with cells surviving at least 8 weeks post-transplantation, producing an improvement of symptoms with regard to neuropathic pain and preventing spinal cord cavitation (Yousefifard et al. 2016). There is a pilot phase I on-going study into the effects of intrathecal injection of autologous MSCs from bone marrow in a small group of human patients with spinal cord injury. Also, there are phase 1/2 and 2a clinical trials of autologous transplantation of mesenchymal stem cells secreting neurotrophic factors in patients with amyotrophic lateral sclerosis, but the results so far are expressed in terms of safety (lack of adverse effects) rather than any measurable beneficial effects (Satti et al. 2016, Petrou et al. 2016).

There have been several reports about the potential of use of allogeneic bone marrow-derived MSCs in patients with severe, treatment-refractory GVHD as a means to inhibit the T- and B-cell mediated immune response (Chen et al. 2015, Hashmi et al. 2016). The results however, remain controversial, with some groups reporting beneficial effects of MSCs treatments and other groups finding no difference in the success rates between patients that received the treatments and controls (Kim et al. 2013).

The capacity for repair of DNA damage and maintenance of genomic integrity is a key factor determining the cell survival under physiological and pathological conditions. A recent study reported that in vitro culturing had significant effects on the capacity of cultured MSCs to repair DNA damage, specifically double strand DNA breaks (DSBs) (Hare et al. 2016). Specifically, the authors of the cited study reported that in cultured MSCs, the efficiency of both mechanisms used for repair of DSBs - homologous recombination (high-fidelity) and nonhomologous end joining (NHEJ, error-prone) declined with repeated passaging. DSBs are believed to be the most toxic, and respectively, the least tolerated of all types of DNA damage. In most types of cells the presence of more than a couple of DSBs is a potent signal for activation of the apoptotic pathways. There are cells where the temporary presence of high levels of DSBs may be normal but it is generally restricted to a specific phase of the life cycle of the cell. In such cases (e.g. immune cells, quiescent oocytes), the mechanisms for activation of DNA damage response pathways may be specifically suppressed or maintained at baseline level only for the duration of the specific phase (Küppers and Dalla-Favera 2001, Petkova et al. 2015). Cultured cells are often subjected to freezing using cryoprotectors with genotoxic potential such as DMSO. Thus, it is possible that the poor survival of transplanted MSCs may be related to a suppression of the mechanisms for repair of toxic DNA lesions in the course of their derivation and culturing. When transplanted at sites of injury, the presence of

inflammation (accompanied with high levels of oxidative stress) may put an additional strain on the already deficient DNA repair system of the MSCs and may accelerate their demise, thereby diminishing their potential to exert their beneficial effects. There is a considerable degree of population polymorphism with regard to genes coding for key proteins of repair of strand breaks such as XRCC2, XRCC3, NBS1 (repair by homologous recombination) and LIG4 and XRCC4 (repair by non-homologous end joining). Typing of MSC lines by the most common polymorphisms in these genes associated with a decreased capacity for repair of DSBs such as XRCC2 rs10234749 (C-to-A), rs6464268 (T-to-C), rs3218373 (G-to-T) and Arg188His (rs3218536); XRCC3 Thr241Met; NBS1 Ile171Val (rs61754966) and Arg215Trp (rs34767364) polymorphisms; LIG4 Thr9Ile (rs1805388), Ile658Val (rs2232641) and the synonymous Asp568Asp polymorphism (C-to-T, rs1805386); the XRCC4 Ala247Ser (rs373409) polymorphism and the pro-apoptotic allele of the TP53 Pro72Arg polymorphism may assist in the selection of MSC lines with superior capacity for DNA repair that may, potentially, exhibit improved survival upon transplantation.

5. The Role of IRC in the Establishment, Maintenance of Pluripotent Stem Cells Used in Research and Potentially Clinical Applications

At present, there are two major types of pluripotent stem cells that are routinely used in research: embryonic stem cells (ESC) and induced pluripotent stem cells (iPSC). Both types are characterised by a proliferative capacity, significantly exceeding the Hayflick's limit for the species and capability of producing all types of differentiated cells that are normally seen in the adult organism. There may be significant ethical issues associated with the research on human ESCs, as the majority of validated methodologies for their derivation are based on the destruction of viable human embryos. In comparison, there is very little ethical controversy about the establishment and use of iPSCs, as they may be derived by differentiated cells by reprogramming back to the pluripotent state. At present, most of the clinically significant types of precursors of differentiated cells (neural progenitors, cardiomyocytes, precursors of osteocytes, chondrocytes, adipocytes and insulin-secreting pancreatic cells, diploid and haploid cells of the spermatocyte lineage, and others) have been successfully derived from murine and human ESC (Phillips 2003, Kroon et al. 2008, Elkabetz and Studer 2008, Jukes et al. 2010, Easley et al. 2012), with the notable exception of human oocyte precursors that proved to be a significant challenge for modern stem cell engineering (Virant-Klun et al. 2011, Petkova et al. 2014a). In a similar fashion, virtually all types of differentiated cells have already been derived from iPSC (Arabadjiev et al. 2014, Yoder 2015, Hossain et al. 2016 ,Hu et al. 2015) gain, derivation of human germline cells form of iPSC presents a problem, unlike murine iPSC-derived germ cell precursors that were shown to differentiate readily into fully functional spermatozoa and oocytes (Ishii 2014).

Differentiated cells derived from pluripotent cells are very valuable in modern research as a model system for the mechanisms of cell proliferation, migration, differentiation, cell-cell

and cell-matrix interactions, cellular senescence and death under physiological and pathological conditions, and they have high potential for future clinical applications (Trifonov et al. 2013, Zhelev 2015, Falconer and Zhelev 2015). Nevertheless, to date very few cell products derived by differentiation of pluripotent cells have been used in any type of officially approved treatment or a clinical trial, mainly because of the inherent risk for induction of cancer growth in the recipient, originating from trace amounts of undifferentiated cells in the cell product (Schwartz et al. 2015, Schulz 2015). Different techniques for identification and elimination of leftover undifferentiated cells have already been developed (Cheng et al. 2012, Christine LaVanne 2013, Wu et al. 2014). Nevertheless, there are two essential problems that may additionally delay the use of preparations derived from pluripotent cells for clinical purposes. One of the problems is related to that fact that until several years ago (and even now) the majority of routinely used pluripotent stem cell lines have been derived and propagated in conditions that impede their further use in any applications in they may be used for treatment of human beings (use of 'homemade' media with undefined and unstandardised composition and/or contact with products of animal origin, such as fetal bovine serum, murine feeders, trypsin from porcine pancreas, etc.) According to a report published in 2012: “...considering the flood of new [ESC] lines in the US and abroad...researchers continue to rely on a few lines derived before the turn of the century" (DeRouen et al. 2012) most all of these lines were created in conditions that could not be described as "xeno-free", the latter being an obligate requirement for any cell product that may potentially be used in treatment of human disease or in human regenerative medicine in order to avoid transmission of infectious agents of animal origin. The second problem is closely related to the first and is also summarised in the quotation cited above. The fact is that most of the present human embryonic stem cell lines available for research have been maintained in culture for a very long time (years and decades). Therefore, this may, through constant passaging, have lost some of their initial characteristics and may have acquired some undesired traits. For example, in 2010 it was reported that the first Swiss ESC line derived only two years previously, in 2008, along with several routinely used hESC lines, exhibited changes consistent with carcinogenic transformation (trisomies for several chromosomes, intrachromosomal loss and gains of genetic material, and other, less conspicuous genomic changes) (Hovatta et al. 2010). Similar genomic rearrangements have been already noticed in other hESC lines that have been kept in culture for years and decades (Draper et al. 2003, Spits et al. 2008). Apparently, genomic instability is a standing problem with ESCs, especially in lines that have been established some time ago. A similar problem may emerge with iPSCs, although being a more recent discovery, the main source of genomic instability may not be the prolonged culturing and repetitive passaging, but rather the effects related to the reprogramming of differentiated cells back to the pluripotent state. iPSC cells exhibit an expression profile overlapping with the expression profile of cancer cells and this may persist even in their differentiated derivatives (Malchenko et al. 2010, Ghosh et al. 2011). Moreover, iPSCs may be more prone to senescence mediated by p53-dependent pathways. The latter were shown to be directly activated in the course of cellular reprogramming by the expression of the major factors used for induction of pluripotency (the Yamanaka factors OCT4, SOX2, KLF4, c-MYC or other combinations) (Banito et al. 2009, Hong et al. 2009). Thus, potential use of existing ESC lines may be associated with

an increased risk for induction of tumorigenesis in the recipient, whereas the use of iPSC may also confer risk for rapid loss of proliferative and differentiation capacity and for shortened lifespan (and respectively, diminished functionality) of the differentiated cell products. For the past few years, many researchers worldwide have recommended that the currently used pluripotent lines may be unsuitable for clinical applications and that establishment of ESC and iPSC lines ought to start anew, in controlled and strictly xeno-free conditions (Lãser et al. 2009,Arabadjiev et al. 2010, Abbasalizadeh and Baharvand 2013, Chakarov et al. 2014c, Desai et al. 2015). Other authors focus their attention upon the mutation rate of stem cell lines and advise that quantitative evaluation of the mutation rate ought to become a routine criterion in assessment of the properties of the pre-existing and the newly established lines and specifically, in the decision-making about its potential suitability for medical applications (Sverdlov and Mineev 2013, Heslop et al. 2015).

The risk in occurrence of mutations and genomic instability in a cultured cell line depends, on the culturing conditions and the number of passages, as well as the intrinsic properties of the cells. ESCs have an inherently high proliferative potential and relatively short doubling time with a shortened G1 phase. The latter means that the severity of the pre-synthetic checkpoints for DNA damage that are particularly important in most dividing cells is relaxed (in human stem cells) or altogether abolished (in rodent stem cells) and as a result, DNA damage may accumulate in the course of rapid division (Arabadjiev et al. 2012). In addition, embryonic stem cells are often treated with various chemical agents (e.g. cryoprotectors such as DMSO) that may have genotoxic properties. In vivo, embryonic cells that have sustained damage beyond a certain threshold are routed towards apoptosis (which may cause the death of the embryo) or may be induced towards differentiation, as the G1/S checkpoints are fully operational in differentiating cells. In vitro however, under conditions specifically designed to maintain the undifferentiated state, embryonic cells that have accumulated significant amounts of damage may lose their proliferation capacity and eventually die, or may find ways to ignore or ignore the mechanisms that dictate that a damaged cell must die - in other words, they may become transformed. Inherent traits that increase the risk for introduction of mutations and/or for increased genomic instability may facilitate the process of transformation. Indeed, the mutation rates in pluripotent stem cells have been shown to be relatively lower than the mutation rates in somatic cells, which are believed to be due at least partly to the extensive use of the mechanism for homologous recombination for DNA repair (Cervantes et al. 2002, Chlon et al. 2016). The latter is less error-prone than the other mechanisms of DNA repair, mainly because it uses the high-accuracy DNA polymerases of replication (Chakarov et al. 2014b). Nevertheless, under conditions where the main checkpoints for presence of DNA damage are virtually non-existent for the duration of many cell divisions, the risk for introduction of alterations in the sequence and structure of DNA may become significant, especially in cell lines that are characterised by inherently low capacity for identification and repair of DNA damage. Carriership of some of the common polymorphisms in genes coding for proteins of DNA repair and maintenance of genome integrity are known to be associated with increased genomic instability in cultured cells - namely, the already mentioned polymorphisms XPC Lys939Gln, XPD Lys751Gln, XRCC3 Thr241 Met and others such as XPG (ERCC5) Asp1104His (rs17655) and XRCC1 Arg399Gln (rs25487) (Vodicka et al. 2004, Petkova et

al. 2013). These, and potentially other polymorphisms in genes coding for products functioning in repair by homologous recombination such as XRCC2 and NBS1, may have specific significance in pluripotent cells relying primarily on homologous recombination to maintain their genome in optimal condition. The C677T polymorphism in the MTHFR gene, which has been shown to be associated with increased risk for cancer in homozygous carriers of the T allele, may also have some significance, as it is very common, the prevalence of the TT genotype reaching 30 % in some populations (Wilcken 2003).

Studies on the individual repair capacity of pre-existing, and specifically, on newly established pluripotent stem cell lines, together with the mutation rate and the general (phenotypic) capacity to repair DNA damage (measured by the rates of unscheduled DNA synthesis) may be of assistance in the selection of pluripotent stem cell lines with optimal characteristics for research purposes. This is especially true for lines that may potentially be used in future clinical applications, in order to decrease the risk of using lines that are inherently prone to carcinogenesis or are likely to deteriorate quickly.

Isolated lack of the expression of the transcription regulator HMGB2 functioning in regulation of DNA repair and maintenance of genomic integrity was found to be associated with increased levels of neurogenesis in brains of adult mice (Abraham et al. 2013). Thus, analysis of the factors modulating the capacity for maintenance of genomic integrity may aid in the development of a potential pathway for stimulation of the neuronal stem cell niche in acute or chronic CNS trauma.

6. Methodologies of IRC Assessment – typing polymorphisms may not be enough to assess the true capacity to repair damage

At present, several dozens of common polymorphisms in genes coding for key proteins responsible for DNA damage identification and repair of genomic integrity have been described and protocols for their rapid typing have been made public. It soon became clear that the strength of the associations of these polymorphisms with human diseases and conditions may be very different in different populations, and in individuals at different ages. While the former could among other things, reflect population-specific intra-genomic interferences between alternative alleles at different loci, the latter was less straightforward and was attributed by some authors to the phenomenon of 'antagonistic pleiotropy', that is the case of one genetic trait being beneficial at early age but deleterious at a later age or vice versa (Khalil et al. 2012a, Chakarov et al. 2014a). There was one notable case in which the same allele of a single-nucleotide polymorphism (ERCC1 C8092A) was associated with opposite effects on the survival of patients with the same disease treated with the same type of agents in two independent large studies (Zhou 2004, Kalikaki et al. 2009). These and similar studies demonstrated that typing of disparate DNA polymorphisms provided incomplete information about individual repair capacity. There is no question that the information gathered from assessment of the status by individual polymorphisms or haplotype analysis is an important part of IRC, but this needs to be integrated within the context of the general phenotype of the individual being tested - that

is, it needed to be augmented by phenotypic analysis. For the purposes of individual assessments, this could conveniently be provided by the already developed methodology of unscheduled (non-replicative) synthesis of DNA, most commonly under conditions of replication blockade (Chakarov et al. 1997, MORI et al. 2000, Marden et al. 2006, Chakarov et al. 2011). For analysis of individual patients, these methods have the relative inconvenience that they require living cells (e.g. fibroblasts) or DNA extracted from living cells, and that tests may need to be repeated in order to monitor the course of a disease or a specific treatment. Nevertheless, since most patients that are for some reason, in need of a transplant of haematopoietic cells or have at some point received a transplant, undertake regular blood analysis in order to monitor their progress. Lymphocytes for assessment of ICR may be made available without additional invasive testing. For freshly collected or cultured cells obtaining a sample for assessment of ICR is unlikely to be an issue.

The individual capacity for repair of DNA damage plays a role in the capacity of stem cells to renew their own population. Therefore, it may be a useful addition to the analyses for selection of cell lines that are likely to be propagated safely, in vitro, without the added risks for loss of the line and/or carcinogenic transformation. Again, this ought to include more than simple typing for common polymorphisms, but also phenotypic markers for proliferation potential, such as telomere length analysis and assessment of telomerase activity (Petkova et al. 2011a, Chakarov et al. 2014a). This type of analysis may have different significance for assessment of the proliferative capacity of ESCs (expressing the catalytic unit of telomerase (telomerase reverse transcriptase, TERT), therefore inherently capable of maintaining telomere length) and for HSCs and MSCs (having limited or virtually non-existent expression of TERT, therefore normally prone to telomere shortening). In any case, assessment of telomere length of freshly derived and cultured stem cells may assist in the selection of cell batches and cell lines with optimal proliferative capacity, avoiding these that may be prone to carcinogenic transformation or these that are at the limit of their proliferative capacity and/or are genetically predisposed to rapid demise with subsequent culturing or after transplantation.

7. Conclusions

Several factors determining the success of a transplantation have been identified, but prognostication of the short-term and long-term outcomes are still unreliable. Individual capacity for repair of DNA damage and maintenance of genomic integrity in the donor and the recipient may account at least partly for the individual variance in the response to conditioning therapies and the associated post-transplantation complications such as GVHD, relapse of the primary disease, shortened survival of transplanted cells in allogeneic environments and the risk for secondary malignancy originating from transplanted cells. Assessments of the individual repair capacity may become a useful tool for selection of the sources for cells for transplantation in order to avoid severe post-transplantation complications, rapid deterioration of the graft and/or induction of cancerous growth. This sub-field of the studies dedicated to the role of individual repair capacity in health and disease is still quite new and a considerable amount of research may be

needed in order to elucidate its role and, potentially, translate the accumulated knowledge into clinical applications.

References

- Abbasalizadeh S, Baharvand H (2013) Technological progress and challenges towards cGMP manufacturing of human pluripotent stem cells based therapeutic products for allogeneic and autologous cell therapies. Biotechnology Advances 31 (8): 1600-1623. DOI: 10.1016/j.biotechadv.2013.08.009
- Abraham A, Bronstein R, Reddy A, Maletic-Savatic M, Aguirre A, Tsirka S (2013) Aberrant Neural Stem Cell Proliferation and Increased Adult Neurogenesis in Mice Lacking Chromatin Protein HMGB2. PLoS ONE 8 (12): e84838. DOI: 10.1371/journal.pone.0084838
- Arabadjiev A, Petkova R, Chakarov S, Pankov R, Zhelev N (2014) We heart cultured hearts. A comparative review of methodologies for targeted differentiation and maintenance of cardiomyocytes derived from pluripotent and multipotent stem cells. Biodiscovery 14 (2): 1. DOI: 10.7750/BioDiscovery.2014.14.2.
- Arabadjiev B, Petkova R, Chakarov S, Momchilova A, Pankov R (2010) Do We Need More Human Embryonic Stem Cell Lines? Biotechnology & Biotechnological Equipment 24 (3): 1921-1927. DOI: 10.2478/v10133-010-0071-x
- Arabadjiev B, Petkova R, Momchilova A, Chakarov S, Pankov R (2012) Of mice and men – differential mechanisms of maintaining the undifferentiated state in mESC and hESC. Biodiscovery 3 (1): 1. DOI: 10.7750/biodiscovery.2012.3.1
- Ara S, Lee PS, Hansen MF, Saya H (1990) Codon 72 polymorphism of the TP53 gene. Nucleic Acids Research 18 (16): 4961-4961. DOI: 10.1093/nar/18.16.4961
- Armitage WJ (2006) The first successful full-thickness corneal transplant: a commentary on Eduard Zirm's landmark paper of 1906. British Journal of Ophthalmology 90 (10): 1222-1223. DOI: 10.1136/bjo.2006.101527
- Arora M, Lindgren B, Basu S, Nagaraj S, Gross M, Weisdorf D, Thyagarajan B (2010) Polymorphisms in the base excision repair pathway and graft-versus-host disease. Leukemia 24 (8): 1470-1475. DOI: 10.1038/leu.2010.139
- Asanuma H, Meldrum D, Meldrum K (2010) Therapeutic Applications of Mesenchymal Stem Cells to Repair Kidney Injury. The Journal of Urology 184 (1): 26-33. DOI: 10.1016/j.juro.2010.03.050
- Baker S, Fearon E, Nigro J, Hamilton S, Preisinger A, Jessup J, vanTuinen P, Ledbetter D, Barker D, Nakamura Y, White R, Vogelstein B (1989) Chromosome 17 deletions and p53 gene mutations in colorectal carcinomas. Science 244 (4901): 217-221. DOI: 10.1126/science.2649981
- Bănescu C, Trifa A, Demian S, Lazar EB, Dima D, Duicu C, Dobreanu M (2014) Polymorphism of XRCC1, XRCC3, and XPD Genes and Risk of Chronic Myeloid Leukemia. BioMed Research International 2014: 1-9. DOI: 10.1155/2014/213790
- Bănescu C, Iancu M, Trifa A, Dobreanu M, Moldovan V, Duicu C, Tripon F, Crauciuc A, Skypnyk C, Bogliș A, Lazar E (2016) Influence of XPC, XPD, XPF, and XPG gene polymorphisms on the risk and the outcome of acute myeloid leukemia in a Romanian population. Tumor Biology 1: 1. DOI: 10.1007/s13277-016-4815-6

- Banito A, Rashid ST, Acosta JC, Li S, Pereira CF, Geti I, Pinho S, Silva JC, Azuara V, Walsh M, Vallier L, Gil J (2009) Senescence impairs successful reprogramming to pluripotent stem cells. Genes & Development 23 (18): 2134-2139. DOI: 10.1101/gad.1811609
- Batar B, Güven M, Barış S, Celkan T, Yıldız İ (2009) DNA repair gene XPD and XRCC1 polymorphisms and the risk of childhood acute lymphoblastic leukemia. Leukemia Research 33 (6): 759-763. DOI: 10.1016/j.leukres.2008.11.005
- Bau D (2009) Single-Nucleotide Polymorphism of the Exo1 Gene: Association with Gastric Cancer Susceptibility and Interaction with Smoking in Taiwan. The Chinese Journal of Physiology 52 (6): 411-418. DOI: 10.4077/cjp.2009.amh076
- Bobadilla-Morales L, Pimentel-Gutiérrez HJ, Gallegos-Castorena S, Paniagua-Padilla JA, Ortega-de-la-Torre C, Sánchez-Zubieta F, Silva-Cruz R, Corona-Rivera JR, Zepeda-Moreno A, González-Ramella O, Corona-Rivera A (2015) Pediatric donor cell leukemia after allogeneic hematopoietic stem cell transplantation in AML patient from related donor. Molecular Cytogenetics 8 (1): 5. DOI: 10.1186/s13039-014-0105-4
- Brunner S, Engelmann MG, Franz W (2008) Stem cell mobilisation for myocardial repair. Expert Opinion on Biological Therapy 8 (11): 1675-1690. DOI: 10.1517/14712598.8.11.1675
- Burjanivova T, Madzo J, Muzikova K, Meyer C, Schneider B, Votava F, Marschalek R, Stary J, Trka J, Zuna J (2006) Prenatal origin of childhood AML occurs less frequently than in childhood ALL. BMC cancer 6: 100. DOI: 10.1186/1471-2407-6-100
- Cervantes R, Stringer J, Shao C, Tischfield J, Stambrook P (2002) Embryonic stem cells and somatic cells differ in mutation frequency and type. Proceedings of the National Academy of Sciences 99 (6): 3586-3590. DOI: 10.1073/pnas.062527199
- Chakarov S, Petkova R, Russev G (2012) p53—Guardian Angel and Archangel. Biotechnology & Biotechnological Equipment 26 (1): 2695-2702. DOI: 10.5504/bbeq.2011.0145
- Chakarov S, Petkova R, Russev G (2014a) Individual capacity for detoxification of genotoxic compounds and repair of DNA damage. Commonly used methods for assessment of capacity for DNA repair. BioDiscovery 11 (2): 1. DOI: 10.7750/biodiscovery.2014.11.2
- Chakarov S, Petkova R, Russev G (2014b) DNA repair systems. BioDiscovery 13 (2): 1. DOI: 10.7750/biodiscovery.2014.13.2
- Chakarov S, Roeva I, Russev G (2011) An Experimental Model for Assessment of Global DNA Repair Capacity. Biotechnology & Biotechnological Equipment 25 (3): 2505-2507. DOI: 10.5504/bbeq.2011.0080
- Chakarov S, Petkova R, Russev G, Zhelev N (2014) DNA repair and carcinogenesis. BioDiscovery 12 (1): 1. DOI: 10.7750/biodiscovery.2014.12.1
- Chakarov S, Stoilov P, Alexandrov A, Russev G (1997) Repair Pattern in the beta-Globin Gene Cluster of Human Fibroblasts after Ultraviolet Irradiation. European Journal of Biochemistry 248 (3): 669-675. DOI: 10.1111/j.1432-1033.1997.00669.x
- Chelenkova P, Petkova R, Chamova T, Zheliazkova-Glaveeva S, Tournev I, Chakarov S (2014) Homozygous carriership of the wildtype allele of the XPCins83 polymorphism is an independent protective factor against cerebrovascular incidents in the Bulgarian population. Compt Rend Acad Bulg Sci 67: 263-268.

- Cheng F, Ke Q, Chen F, Cai B, Gao Y, Ye C, Wang D, Zhang L, Lahn BT, Li W, Xiang AP (2012) Protecting against wayward human induced pluripotent stem cells with a suicide gene. Biomaterials 33 (11): 3195-204. DOI: 10.1016/j.biomaterials.2012.01.023
- Chen X, Wang C, Yin J, Xu J, Wei J, Zhang Y (2015) Efficacy of Mesenchymal Stem Cell Therapy for Steroid-Refractory Acute Graft-Versus-Host Disease following Allogeneic Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-Analysis. PLOS ONE 10 (8): e0136991. DOI: 10.1371/journal.pone.0136991
- Cherdyntseva NV, Gervas PA, Litvyakov NV, Stakcheeva MN, Ponomaryeva AA, Dobrodeev AY, Denisov EV, Belyavskaya VA, Choinzonov EL (2010) Age-related function of tumor suppressor gene TP53:contribution to cancer risk and progression. Experimental oncology 32 (3): 205-8.
- Chlon T, Ruiz-Torres S, Maag L, Mayhew C, Wikenheiser-Brokamp K, Davies S, Mehta P, Myers K, Wells J, Wells S (2016) Overcoming Pluripotent Stem Cell Dependence on the Repair of Endogenous DNA Damage. Stem Cell Reports 6 (1): 44-54. DOI: 10.1016/j.stemcr.2015.12.001
- Christine LaVanne MM (2013) Safeguarding Stem Cell-Based Regenerative Therapy against Iatrogenic Cancerogenesis: Transgenic Expression of DNASE1, DNASE1L3, DNASE2,DFFB Controlled By POLA1 Promoter in Proliferating and Directed Differentiation Resisting Human. Journal of Stem Cell Research & Therapy 9 (5): 1. DOI: 10.4172/2157-7633.s9-005
- CLEAVER JE (1968) Defective Repair Replication of DNA in Xeroderma Pigmentosum. Nature 218 (5142): 652-656. DOI: 10.1038/218652a0
- Coppedè F, Migliore L (2015) DNA damage in neurodegenerative diseases. Mutat Res 776: 84-97.
- Cosset JM (2002) ESTRO Breur Gold Medal Award Lecture 2001: Irradiation accidents – lessons for oncology? Radiotherapy and Oncology 63 (1): 1-10. DOI: 10.1016/s0167-8140(02)00059-2
- DAUSSET J, BRECY H (1957) Identical Nature of the Leucocyte Antigens detectable in Monozygotic Twins by means of Immune Iso-Leuco-agglutinins. Nature 180 (4599): 1430-1430. DOI: 10.1038/1801430a0
- DeRouen M, McCormick J, Owen-Smith J, Scott CT (2012) The Race Is On: Human Embryonic Stem Cell Research Goes Global. Stem Cell Reviews and Reports 8 (4): 1043-1047. DOI: 10.1007/s12015-012-9391-6
- Desai A, Qing Y, Gerson S (2014) Exonuclease 1 is a Critical Mediator of Survival During DNA Double Strand Break Repair in Nonquiescent Hematopoietic Stem and Progenitor Cells. STEM CELLS 32 (2): 582-593. DOI: 10.1002/stem.1596
- Desai N, Rambhia P, Gishto A (2015) Human embryonic stem cell cultivation: historical perspective and evolution of xeno-free culture systems. Reproductive Biology and Endocrinology 13 (1): 9. DOI: 10.1186/s12958-015-0005-4
- Diamond H, Ornellas M, Orfao A, Gomes BE, Campos MM, Fernandez TS, da Silva RI, Alves G, Lage C, da Silva DA, Moellmann-Coelho A, da Cruz GS, Bouzas L, Abdelhay E (2011) Acute myeloid leukemia of donor origin after allogeneic stem cell transplantation from a sibling who harbors germline XPD and XRCC3 homozygous polymorphisms. Journal of Hematology & Oncology 4 (1): 39. DOI: 10.1186/1756-8722-4-39
- Dominici M, Blanc KL, Mueller I, Slaper-Cortenbach I, Marini FC, Krause DS, Deans RJ, Keating A, Prockop DJ, Horwitz EM (2006) Minimal criteria for defining multipotent

mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 8 (4): 315-317. DOI: 10.1080/14653240600855905

- Do T, Ucisik-Akkaya E, Davis C, Morrison B, Dorak MT (2009) TP53 R72P and MDM2 SNP309 polymorphisms in modification of childhood acute lymphoblastic leukemia susceptibility. Cancer Genetics and Cytogenetics 195 (1): 31-36. DOI: 10.1016/j.cancergencyto.2009.05.009
- Draper JS, Smith K, Gokhale P, Moore HD, Maltby E, Johnson J, Meisner L, Zwaka TP, Thomson JA, Andrews PW (2003) Recurrent gain of chromosomes 17q and 12 in cultured human embryonic stem cells. Nature Biotechnology 22 (1): 53-54. DOI: 10.1038/nbt922
- Easley C, Phillips B, McGuire M, Barringer J, Valli H, Hermann B, Simerly C, Rajkovic A, Miki T, Orwig K, Schatten G (2012) Direct Differentiation of Human Pluripotent Stem Cells into Haploid Spermatogenic Cells. Cell Reports 2 (3): 440-446. DOI: 10.1016/j.celrep.2012.07.015
- Elkabetz Y, Studer L (2008) Human ESC-derived Neural Rosettes and Neural Stem Cell Progression. Cold Spring Harbor Symposia on Quantitative Biology 73: 377-387. DOI: 10.1101/sqb.2008.73.052
- Enjuanes A, Benavente Y, Bosch F, Martin-Guerrero I, Colomer D, Perez-Alvarez S, Reina O, Ardanaz MT, Jares P, Garcia-Orad A, Pujana MA, Montserrat E, Sanjose Sd, Campo E (2008) Genetic Variants in Apoptosis and Immunoregulation-Related Genes Are Associated with Risk of Chronic Lymphocytic Leukemia. Cancer Research 68 (24): 10178-10186. DOI: 10.1158/0008-5472.can-08-2221
- Falconer K, Zhelev N (2015) Evaluating the effect of piceatannol in cardiac hypertrophy in human stem-cell-derived cardiomyocytes. BioDiscovery 16: 2. DOI: 10.7750/biodiscovery.2015.16.2
- Fung Y, Murphree A, T'Ang A, Qian J, Hinrichs S, Benedict W (1987) Structural evidence for the authenticity of the human retinoblastoma gene. Science 236 (4809): 1657-1661. DOI: 10.1126/science.2885916
- Gale KB, Ford AM, Repp R, Borkhardt A, Keller C, Eden OB, Greaves MF (1997) Backtracking leukemia to birth: Identification of clonotypic gene fusion sequences in neonatal blood spots. Proceedings of the National Academy of Sciences 94 (25): 13950-13954. DOI: 10.1073/pnas.94.25.13950
- Gavande N, VanderVere-Carozza P, Hinshaw H, Jalal S, Sears C, Pawelczak K, Turchi J (2016) DNA repair targeted therapy: The past or future of cancer treatment? Pharmacology & Therapeutics 160: 65-83. DOI: 10.1016/j.pharmthera.2016.02.003
- Ghosh Z, Huang M, Hu S, Wilson KD, Dey D, Wu JC (2011) Dissecting the Oncogenic and Tumorigenic Potential of Differentiated Human Induced Pluripotent Stem Cells and Human Embryonic Stem Cells. Cancer Research 71 (14): 5030-5039. DOI: 10.1158/0008-5472.can-10-4402
- Gibbons R (2005) Cord Blood. The National Academies Press, 1 pp. URL: http://dx.doi.org/10.17226/11269 DOI: 10.17226/11269
- Gruhn B, Taub JW, Ge Y, Beck JF, Zell R, Häfer R, Hermann FH, Debatin K, Steinbach D (2008) Prenatal origin of childhood acute lymphoblastic leukemia, association with birth weight and hyperdiploidy. Leukemia 22 (9): 1692-1697. DOI: 10.1038/leu.2008.152
- Gyongyosi M, Blanco J, Marian T, Tron L, Petnehazy O, Petrasi Z, Hemetsberger R, Rodriguez J, Font G, Pavo IJ, Kertesz I, Balkay L, Pavo N, Posa A, Emri M, Galuska L, Kraitchman DL, Wojta J, Huber K, Glogar D (2008) Serial Noninvasive In Vivo Positron

Emission Tomographic Tracking of Percutaneously Intramyocardially Injected Autologous Porcine Mesenchymal Stem Cells Modified for Transgene Reporter Gene Expression. Circulation: Cardiovascular Imaging 1 (2): 94-103. DOI: 10.1161/circimaging.108.797449

- Haenszel W, Taeuber K (1964) Lung-cancer mortality as related to residence and smoking histories. II. White females. J Natl Cancer Inst 32: 803-838.
- Haenszel W, Loveland D, Sirken M (1962) Lung-cancer mortality as related to residence and smoking histories. I. White males. J Natl Cancer Inst 28: 947-1001.
- Haghighi MM, Taleghani MY, Mohebbi SR, Vahedi M, Fatemi SR, Zali N, Shemirani AI, Zali MR (2010) Impact of EXO1 Polymorphism in Susceptibility to Colorectal Cancer. Genetic Testing and Molecular Biomarkers 14 (5): 649-652. DOI: 10.1089/gtmb.2010.0034
- Hamdy MS, El-Haddad AM, Bahaa El-Din NM, Makhlouf MM, Abdel-Hamid SM (2011) RAD51 and XRCC3 gene polymorphisms and the risk of developing acute myeloid leukemia. Journal of investigative medicine : the official publication of the American Federation for Clinical Research 59 (7): 1124-30. DOI: 10.231/JIM.0b013e3182281da3
- Hare I, Gencheva M, Evans R, Fortney J, Piktel D, Vos J, Howell D, Gibson L (2016) In VitroExpansion of Bone Marrow Derived Mesenchymal Stem Cells Alters DNA Double Strand Break Repair of Etoposide Induced DNA Damage. Stem Cells International 2016: 1-11. DOI: 10.1155/2016/8270464
- Hashmi S, Ahmed M, Murad MH, Litzow MR, Adams RH, Ball LM, Prasad VK, Kebriaei P, Ringden O (2016) Survival after mesenchymal stromal cell therapy in steroid-refractory acute graft-versus-host disease: systematic review and meta-analysis. The Lancet Haematology 3 (1): e45-e52. DOI: 10.1016/s2352-3026(15)00224-0
- Heslop JA, Hammond TG, Santeramo I, Piella AT, Hopp I, Zhou J, Baty R, Graziano EI, Marco BP, Caron A, Skold P, Andrews PW, Baxter MA, Hay DC, Hamdam J, Sharpe ME, Patel S, Jones DR, Reinhardt J, Danen EHJ, Ben-David U, Stacey G, Bjorquist P, Piner J, Mills J, Rowe C, Pellegrini G, Sethu S, Antoine DJ, Cross MJ, Murray P, Williams DP, Kitteringham NR, Goldring CEP, Park BK (2015) Concise Review: Workshop Review: Understanding and Assessing the Risks of Stem Cell-Based Therapies. Stem Cells Translational Medicine 4 (4): 389-400. DOI: 10.5966/sctm.2014-0110
- Hofmann M (2005) Monitoring of Bone Marrow Cell Homing Into the Infarcted Human Myocardium. Circulation 111 (17): 2198-2202. DOI: 10.1161/01.cir.0000163546.27639.aa
- Hong H, Takahashi K, Ichisaka T, Aoi T, Kanagawa O, Nakagawa M, Okita K, Yamanaka S (2009) Suppression of induced pluripotent stem cell generation by the p53–p21 pathway. Nature 460 (7259): 1132-1135. DOI: 10.1038/nature08235
- Hossain MK, Dayem AA, Han J, Saha SK, Yang G, Choi H, Cho S (2016) Recent Advances in Disease Modeling and Drug Discovery for Diabetes Mellitus Using Induced Pluripotent Stem Cells. International Journal of Molecular Sciences 17 (2): 256. DOI: 10.3390/ijms17020256
- Hovatta O, Jaconi M, Töhönen V, Béna F, Gimelli S, Bosman A, Holm F, Wyder S, Zdobnov E, Irion O, Andrews P, Antonarakis S, Zucchelli M, Kere J, Feki A (2010) A Teratocarcinoma-Like Human Embryonic Stem Cell (hESC) Line and Four hESC Lines Reveal Potentially Oncogenic Genomic Changes. PLoS ONE 5 (4): e10263. DOI: 10.1371/journal.pone.0010263

- Hu W, He Y, Xiong Y, Lu H, Chen H, Hou L, Qiu Z, Fang Y, Zhang S (2015) Derivation, Expansion, and Motor Neuron Differentiation of Human-Induced Pluripotent Stem Cells with Non-Integrating Episomal Vectors and a Defined Xenogeneic-free Culture System. Molecular Neurobiology 53 (3): 1589-1600. DOI: 10.1007/s12035-014-9084-z
- Ishii T (2014) Human iPS Cell-Derived Germ Cells: Current Status and Clinical Potential. Journal of Clinical Medicine 3 (4): 1064-1083. DOI: 10.3390/jcm3041064
- Jacobsohn DA, Vogelsang GB (2007) Acute graft versus host disease. Orphanet J Rare Dis 2: 35.
- Jin G, Wang H, Hu Z, Liu H, Sun W, Ma H, Chen D, Miao R, Tian T, Jin L, Wei Q, Huang W, Lu D, Shen H (2008) Potentially functional polymorphisms of EXO1 and risk of lung cancer in a Chinese population: A case-control analysis. Lung Cancer 60 (3): 340-346. DOI: 10.1016/j.lungcan.2007.11.003
- Jukes J, van Blitterswijk C, Boer Jd (2010) Skeletal tissue engineering using embryonic stem cells. Journal of Tissue Engineering and Regenerative Medicine 4 (3): 165-180. DOI: 10.1002/term.234
- Kalikaki A, Kanaki M, Vassalou H, Souglakos J, Voutsina A, Georgoulias V, Mavroudis D (2009) DNA Repair Gene Polymorphisms Predict Favorable Clinical Outcome in Advanced Non–Small-Cell Lung Cancer. Clinical Lung Cancer 10 (2): 118-123. DOI: 10.3816/clc.2009.n.015
- Kamada T, Koda M, Dezawa M, Yoshinaga K, Hashimoto M, Koshizuka S, Nishio Y, Moriya H, Yamazaki M (2005) Transplantation of Bone Marrow Stromal Cell-Derived Schwann Cells Promotes Axonal Regeneration and Functional Recovery after Complete Transection of Adult Rat Spinal Cord. Journal of Neuropathology & Experimental Neurology 64 (1): 37-45. DOI: 10.1093/jnen/64.1.37
- Kan C, Zhang J (2015) BRCA1 Mutation: A Predictive Marker for Radiation Therapy? International Journal of Radiation Oncology*Biology*Physics 93 (2): 281-293. DOI: 10.1016/j.ijrobp.2015.05.037
- Khalil H, Petkova R, Zhelev N (2012a) Differential Genetic Advantages in Youth and in Aging, or How to Die Healthy. Biotechnology & Biotechnological Equipment 26 (1): 2703-2711. DOI: 10.5504/bbeq.2011.0151
- Khalil H, Tummala H, Zhelev N (2012b) ATM in focus: A damage sensor and cancer target. BioDiscovery 5: 1. DOI: 10.7750/biodiscovery.2012.5.1
- Khalil H, Tummala H, Chakarov S, Zhelev N, Lane D (2012c) Targeting ATM pathway for therapeutic intervention in cancer. Biodiscovery 1: 1. DOI: 10.7750/biodiscovery.2012.1.3
- Khalil HS, Tummala H, Hupp TR, Zhelev N (2012) Pharmacological inhibition of ATM by KU55933 stimulates ATM transcription. Experimental Biology and Medicine 237 (6): 622-634. DOI: 10.1258/ebm.2012.011378
- Kiel G (1978) The history of plastic surgery (author's transl). Laryngol Rhinol Otol (Stuttg) 57: 581-591.
- Kim N, Im K, Lim J, Jeon E, Nam Y, Kim E, Cho S (2013) Mesenchymal stem cells for the treatment and prevention of graft-versus-host disease: experiments and practice. Annals of Hematology 92 (10): 1295-1308. DOI: 10.1007/s00277-013-1796-z
- Kornblit B, Masmas T, Petersen S, Madsen H, Heilmann C, Schejbel L, Sengeløv H, Müller K, Garred P, Vindeløv L (2010) Association of HMGB1 Polymorphisms with Outcome after Allogeneic Hematopoietic Cell Transplantation. Biology of Blood and Marrow Transplantation 16 (2): 239-252. DOI: 10.1016/j.bbmt.2009.10.002

- Kroon E, Martinson LA, Kadoya K, Bang AG, Kelly OG, Eliazer S, Young H, Richardson M, Smart NG, Cunningham J, Agulnick AD, D'Amour KA, Carpenter MK, Baetge EE (2008) Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. Nature Biotechnology 26 (4): 443-452. DOI: 10.1038/nbt1393
- Küppers R, Dalla-Favera R (2001) Mechanisms of chromosomal translocations in B cell lymphomas. Oncogene 20 (40): 5580-5594. DOI: 10.1038/sj.onc.1204640
- Lãser P, Schirm J, Guhr A, Wobus A, Kurtz A (2009) Human Embryonic Stem Cell Lines and their Use in International Research. STEM CELLS 28: 240-246. DOI: 10.1002/stem.286
- Lee S, Choi E, Cha M, Hwang K (2015) Cell Adhesion and Long-Term Survival of Transplanted Mesenchymal Stem Cells: A Prerequisite for Cell Therapy. Oxidative Medicine and Cellular Longevity 2015: 1-9. DOI: 10.1155/2015/632902
- Leung W, Campana D, Yang J, Pei D, Coustan-Smith E, Gan K, Rubnitz JE, Sandlund JT, Ribeiro RC, Srinivasan A, Hartford C, Triplett BM, Dallas M, Pillai A, Handgretinger R, Laver JH, Pui C- (2011) High success rate of hematopoietic cell transplantation regardless of donor source in children with very high-risk leukemia. Blood 118 (2): 223-230. DOI: 10.1182/blood-2011-01-333070
- Li Q, Huang L, Rong L, Xue Y, Lu Q, Rui Y, Li J, Tong N, Wang M, Zhang Z, Fang Y (2011) hOGG1 Ser326Cys polymorphism and risk of childhood acute lymphoblastic leukemia in a Chinese population. Cancer Science 102 (6): 1123-1127. DOI: 10.1111/j.1349-7006.2011.01928.x
- Malchenko S, Galat V, Seftor E, Vanin E, Costa F, Seftor RB, Soares M, Hendrix MC (2010) Cancer hallmarks in induced pluripotent cells: New insights. Journal of Cellular Physiology 225 (2): 390-393. DOI: 10.1002/jcp.22280
- Malkin D, Li F, Strong L, Fraumeni J, Nelson C, Kim D, Kassel J, Gryka M, Bischoff F, Tainsky M, et a (1990) Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 250 (4985): 1233-1238. DOI: 10.1126/science.1978757
- Marden A, Walmsley R, Schweizer L, Schweizer M (2006) Yeast-based assay for the measurement of positive and negative influences on microsatellite stability. FEMS Yeast Research 6 (5): 716-725. DOI: 10.1111/j.1567-1364.2006.00092.x
- Matsunaga T, Murase K, Yoshida M, Fujimi A, Iyama S, Kuribayashi K, Sato T, Kogawa K, Hirayama Y, Sakamaki S, Kohda K, Niitsu Y (2005) Donor cell derived acute myeloid leukemia after allogeneic cord blood transplantation in a patient with adult T-cell lymphoma. American Journal of Hematology 79 (4): 294-298. DOI: 10.1002/ajh.20349
- McGraw KL, Zhang LM, Rollison DE, Basiorka AA, Fulp W, Rawal B, Jerez A, Billingsley DL, Lin H, Kurtin SE, Yoder S, Zhang Y, Guinta K, Mallo M, Solé F, Calasanz MJ, Cervera J, Such E, González T, Nevill TJ, Haferlach T, Smith AE, Kulasekararaj A, Mufti G, Karsan A, Maciejewski JP, Sokol L, Epling-Burnette PK, Wei S, List AF (2015) The relationship of TP53 R72P polymorphism to disease outcome and TP53 mutation in myelodysplastic syndromes. Blood Cancer Journal 5 (3): e291. DOI: 10.1038/bcj.2015.11
- Mori H, Colman SM, Xiao Z, Ford AM, Healy LE, Donaldson C, Hows JM, Navarrete C, Greaves M (2002) Chromosome translocations and covert leukemic clones are generated during normal fetal development. Proceedings of the National Academy of Sciences 99 (12): 8242-8247. DOI: 10.1073/pnas.112218799

- MORI M, KOBAYASHI H, NAGANUMA M, SUGIYAMA C, KATSUMURA Y, FURIHATA C (2000) Induction of unscheduled DNA synthesis in hairless mouse epidermis by ultraviolet light. The Journal of Toxicological Sciences 25 (1): 17-24. DOI: 10.2131/jts.25.17
- Nakano M, Kodama Y, Ohtaki K, Itoh M, Awa AA, Cologne J, Kusunoki Y, Nakamura N (2004) Estimating the Number of Hematopoietic or Lymphoid Stem Cells Giving Rise to Clonal Chromosome Aberrations in Blood T Lymphocytes. Radiation Research 161 (3): 273-281. DOI: 10.1667/rr3133
- Nayyar A, Chakalova L (2015) APOE4, oxidative stress and decreased repair capacity - a no-brainer. Faulty lipid metabolism and increased levels of oxidative damage may be risk factors in the pathogenesis of late-onset dementia. BioDiscovery 17: 1. DOI: 10.7750/biodiscovery.2015.17.1
- Neglia J, Meadows A, Robison L, Kim T, Newton W, Ruymann F, Sather H, Hammond GD (1991) Second Neoplasms after Acute Lymphoblastic Leukemia in Childhood. New England Journal of Medicine 325 (19): 1330-1336. DOI: 10.1056/nejm199111073251902
- Passweg JR, Baldomero H, Bader P, Bonini C, Cesaro S, Dreger P, Duarte RF, Dufour C, Kuball J, Farge-Bancel D, Gennery A, Kröger N, Lanza F, Nagler A, Sureda A, Mohty M (2016) Hematopoietic stem cell transplantation in Europe 2014: more than 40 000 transplants annually. Bone Marrow Transplantation 1: 1-7. DOI: 10.1038/bmt.2016.20
- Payne, Hackel (1961) Inheritance of human leukocyte antigens. Am J Hum Genet 13: 306-319.
- Pereira WC, Khushnooma I, Madkaikar M, Ghosh K (2008) Reproducible methodology for the isolation of mesenchymal stem cells from human umbilical cord and its potential for cardiomyocyte generation. Journal of Tissue Engineering and Regenerative Medicine 2 (7): 394-399. DOI: 10.1002/term.107
- Pero R, Östlund C (1980) Direct comparison, in human resting lymphocytes, of the inter-individual variations in unscheduled DNA synthesis induced by N-acetoxy-2-acetylaminofluorene and ultraviolet irradiation. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis 73 (2): 349-361. DOI: 10.1016/0027-5107(80)90200-6
- Pero R, Bryngelsson C, Mitelman F, Kornfält R, Thulin T, Norden Å (1978) Interindividual variation in the responses of cultured human lymphocytes to exposure from DNA damaging chemical agents. Mutation Research/Environmental Mutagenesis and Related Subjects 53 (3): 327-341. DOI: 10.1016/0165-1161(78)90005-5
- Petkova R, Chicheva Z, Chakarov S (2011a) Measuring Telomere Length—From Ends to Means. Biotechnology & Biotechnological Equipment 25 (4): 2576-2582. DOI: 10.5504/bbeq.2011.0103
- Petkova R, Tummala H, Zhelev N (2011b) Nothing in Excess—Lessons Learned from the Expression of High-Mobility Group Proteins Type a in Non-Cancer and Cancer Cells. Biotechnology & Biotechnological Equipment 25 (4): 2572-2575. DOI: 10.5504/bbeq.2011.0102
- Petkova R, Arabadjiev B, Chakarov S, Pankov R (2014) Current state of the opportunities for derivation of germ-like cells from pluripotent stem cells: are you a man, or a mouse? Biotechnology & Biotechnological Equipment 28 (2): 184-191. DOI: 10.1080/13102818.2014.907037

- Petkova R, Chelenkova P, Georgieva E, Chakarov S (2013) What's Your Poison? Impact of Individual Repair Capacity on the Outcomes of Genotoxic Therapies in Cancer. Part I —Role of Individual Repair Capacity in the Constitution of Risk for Late-Onset Multifactorial Disease. Biotechnology & Biotechnological Equipment 27 (6): 4208-4216. DOI: 10.5504/bbeq.2013.0097
- Petkova R, Chelenkova P, Georgieva E, Chakarov S (2014) What's your poison? Impact of individual repair capacity on the outcomes of genotoxic therapies in cancer. Part II – information content and validity of biomarkers for individual repair capacity in the assessment of outcomes of anticancer therapy. Biotechnology & Biotechnological Equipment 28 (1): 2-7. DOI: 10.1080/13102818.2014.902532
- Petkova R, Dimitrova V, Zhelev N, Chakarov S (2015) Reproductive outcomes in pregnant women aged 35 or older: the role of individual repair capacity. BioDiscovery 1: 2. DOI: 10.7750/biodiscovery.2015.18.2
- Petrou P, Gothelf Y, Argov Z, Gotkine M, Levy Y, Kassis I, Vaknin-Dembinsky A, Ben-Hur T, Offen D, Abramsky O, Melamed E, Karussis D (2016) Safety and Clinical Effects of Mesenchymal Stem Cells Secreting Neurotrophic Factor Transplantation in Patients With Amyotrophic Lateral Sclerosis. JAMA Neurology 73 (3): 337. DOI: 10.1001/jamaneurol.2015.4321
- Phillips B (2003) Differentiation of embryonic stem cells for pharmacological studies on adipose cells. Pharmacological Research 47 (4): 263-268. DOI: 10.1016/s1043-6618(03)00035-5
- Poncelet A, Hiel A, Vercruysse J, Hermans D, Zech F, Gianello P (2010) Intracardiac allogeneic mesenchymal stem cell transplantation elicits neo-angiogenesis in a fully immunocompetent ischaemic swine model☆. European Journal of Cardio-Thoracic Surgery 38 (6): 781-787. DOI: 10.1016/j.ejcts.2010.03.035
- Roy LM, Jaruga P, Wood TG, McCullough AK, Dizdaroglu M, Lloyd RS (2007) Human Polymorphic Variants of the NEIL1 DNA Glycosylase. Journal of Biological Chemistry 282 (21): 15790-15798. DOI: 10.1074/jbc.m610626200
- SABTY FA, DEMECKOVA E, BOJTAROVA E, HRUBISKO M, MISTRIK M (2012) Is there still a role for autologous stem cell transplantation in acute myeloid leukemia? Neoplasma 60 (2): 167-173. DOI: 10.4149/neo_2013_022
- Satti HS, Waheed A, Ahmed P, Ahmed K, Akram Z, Aziz T, Satti TM, Shahbaz N, Khan MA, Malik SA (2016) Autologous mesenchymal stromal cell transplantation for spinal cord injury: A Phase I pilot study. Cytotherapy 18 (4): 518-522. DOI: 10.1016/j.jcyt.2016.01.004
- Schiewer M, Knudsen K (2016) Linking DNA Damage and Hormone Signaling Pathways in Cancer. Trends in Endocrinology & Metabolism 27 (4): 216-225. DOI: 10.1016/j.tem.2016.02.004
- Schulz TC (2015) Concise Review: Manufacturing of Pancreatic Endoderm Cells for Clinical Trials in Type 1 Diabetes. Stem Cells Translational Medicine 4 (8): 927-931. DOI: 10.5966/sctm.2015-0058
- Schwartz SD, Regillo CD, Lam BL, Eliott D, Rosenfeld PJ, Gregori NZ, Hubschman J, Davis JL, Heilwell G, Spirn M, Maguire J, Gay R, Bateman J, Ostrick RM, Morris D, Vincent M, Anglade E, Del Priore LV, Lanza R (2015) Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. The Lancet 385 (9967): 509-516. DOI: 10.1016/s0140-6736(14)61376-3

- Serna DS (2003) Trends in Survival Rates After Allogeneic Hematopoietic Stem-Cell Transplantation for Acute and Chronic Leukemia by Ethnicity in the United States and Canada. Journal of Clinical Oncology 21 (20): 3754-3760. DOI: 10.1200/jco.2003.03.133
- Spits C, Mateizel I, Geens M, Mertzanidou A, Staessen C, Vandeskelde Y, Van der Elst J, Liebaers I, Sermon K (2008) Recurrent chromosomal abnormalities in human embryonic stem cells. Nature Biotechnology 26 (12): 1361-1363. DOI: 10.1038/nbt.1510
- Sun Y, Chen L, Hou X, Hou W, Dong J, Sun L, Tang K, Wang B, Song J, Li H, Wang K (2007) Differentiation of bone marrow-derived mesenchymal stem cells from diabetic patients into insulin-producing cells in vitro. Chinese medical journal 120 (9): 771-6.
- Sverdlov E, Mineev K (2013) Mutation rate in stem cells: an underestimated barrier on the way to therapy. Trends in Molecular Medicine 19 (5): 273-280. DOI: 10.1016/j.molmed.2013.01.004
- Tang J, Wang J, Yang J, Kong X, Zheng F, Guo L, Zhang L, Huang Y (2009) Mesenchymal stem cells over-expressing SDF-1 promote angiogenesis and improve heart function in experimental myocardial infarction in rats☆. European Journal of Cardio-Thoracic Surgery 36 (4): 644-650. DOI: 10.1016/j.ejcts.2009.04.052
- Thomas M, Kalita A, Labrecque S, Pim D, Banks L, Matlashewski G (1999) Two Polymorphic Variants of Wild-Type p53 Differ Biochemically and Biologically. Molecular and Cellular Biology 19 (2): 1092-1100. DOI: 10.1128/mcb.19.2.1092
- Thyagarajan B, Lindgren B, Basu S, Nagaraj S, Gross M, Weisdorf D, Arora M (2010) Association between Genetic Variants in the Base Excision Repair Pathway and Outcomes after Hematopoietic Cell Transplantations. Biology of Blood and Marrow Transplantation 16 (8): 1084-1089. DOI: 10.1016/j.bbmt.2010.03.001
- Toma C (2002) Human Mesenchymal Stem Cells Differentiate to a Cardiomyocyte Phenotype in the Adult Murine Heart. Circulation 105 (1): 93-98. DOI: 10.1161/hc0102.101442
- Trifonov D, Tummala H, Clements S, Zhelev N (2013) Effect of roscovitine on cardiac hypertrophy in human stem cell derived cardiomyocytes. Current Opinion in Biotechnology 24: S114-S115. DOI: 10.1016/j.copbio.2013.05.354
- Tummala H, Goltsov A, Khalil H, Sproul A, Scott F, Mitev V, Zhelev N (2012) Advocating the need of a systems biology approach for personalised prognosis and treatment of B-CLL patients. BioDiscovery 6: 1. DOI: 10.7750/biodiscovery.2012.6.4
- Valenzuela MT, Guerrero R, Núñez MI, de Almodóvar JMR, Sarker M, Murcia Gd, Oliver FJ (2002) PARP-1 modifies the effectiveness of p53-mediated DNA damage response. Oncogene 21 (7): 1108-1116. DOI: 10.1038/sj.onc.1205169
- Velic D, Couturier A, Ferreira M, Rodrigue A, Poirier G, Fleury F, Masson J (2015) DNA Damage Signalling and Repair Inhibitors: The Long-Sought-After Achilles' Heel of Cancer. Biomolecules 5 (4): 3204-3259. DOI: 10.3390/biom5043204
- Virant-Klun I, Stimpfel M, Skutella T (2011) Ovarian pluripotent/multipotent stem cells and in vitro oogenesis in mammals. Histology and histopathology 26 (8): 1071-82.
- Vodicka P, Kumar R, Stetina R, Sanyal S, Soucek P, Haufroid V, Dusinska M, Kuricova M, Zamecnikova M, Musak L, Buchancova J, Norppa H, Hirvonen A, Vodickova L, Naccarati A, Matousu Z, Hemminki K (2004) Genetic polymorphisms in DNA repair genes and possible links with DNA repair rates, chromosomal aberrations and single-strand breaks in DNA. Carcinogenesis 25: 757-763. DOI: 10.1093/carcin/bgh064

- Wang Y, Cortez D, Yazdi P, Neff N, Elledge SJ, Qin J (2000) BASC, a super complex of BRCA1-associated proteins involved in the recognition and repair of aberrant DNA structures. Genes & development 14 (8): 927-39. URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC316544
- Weber MH, Wenzel U, Thiel E, Knauf WU (2000) Chromosomal Aberrations Characteristic for sAML/sMDS Are Not Detectable by Random Screening Using FISH in Peripheral Blood-Derived Grafts Used for Autologous Transplantation. Journal of Hematotherapy & Stem Cell Research 9 (6): 861-865. DOI: 10.1089/152581600750062291
- Wilcken B (2003) Geographical and ethnic variation of the 677C>T allele of 5,10 methylenetetrahydrofolate reductase (MTHFR): findings from over 7000 newborns from 16 areas world wide. Journal of Medical Genetics 40 (8): 619-625. DOI: 10.1136/jmg.40.8.619
- Wu C, Hong SG, Winkler T, Spencer DM, Jares A, Ichwan B, Nicolae A, Guo V, Larochelle A, Dunbar CE (2014) Development of an inducible caspase-9 safety switch for pluripotent stem cell–based therapies. Molecular Therapy — Methods & Clinical Development 1: 14053. DOI: 10.1038/mtm.2014.53
- Wu H, Roks AM (2014) Genomic instability and vascular aging: A focus on nucleotide excision repair. Trends in Cardiovascular Medicine 24 (2): 61-68. DOI: 10.1016/j.tcm.2013.06.005
- Xu P, Chen B, Feng J, Cheng L, Xia G, Li Y, Qian J, Ding J, Lu Z (2012) Polymorphisms in XPC provide prognostic information in acute myeloid leukemia. International Journal of Hematology 96 (4): 450-460. DOI: 10.1007/s12185-012-1145-3
- Yoder M (2015) Differentiation of pluripotent stem cells into endothelial cells. Curr Opin Hematol 22: 252-257.
- Yousefifard M, Nasirinezhad F, Manaheji HS, Janzadeh A, Hosseini M, Keshavarz M (2016) Human bone marrow-derived and umbilical cord-derived mesenchymal stem cells for alleviating neuropathic pain in a spinal cord injury model. Stem Cell Research & Therapy 7 (1): 36. DOI: 10.1186/s13287-016-0295-2
- Zhelev N (2015) Novel stem-cell-based approaches in the development of cyclin-dependent kinase inhibitors as new therapeutics in cardiology. Journal of Biotechnology & Biomaterials 05 (2): 32. DOI: 10.4172/2155-952x.s1.033
- Zhou W (2004) Excision Repair Cross-Complementation Group 1 Polymorphism Predicts Overall Survival in Advanced Non-Small Cell Lung Cancer Patients Treated With Platinum-Based Chemotherapy. Clinical Cancer Research 10 (15): 4939-4943. DOI: 10.1158/1078-0432.ccr-04-0247